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REVIEW

Systemic Therapy in Advanced Hepatocellular Carcinoma: Patient Selection and Key Considerations

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Abstract: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide. Most patients with HCC have advanced disease at initial diagnosis, and sorafenib has been the only systemic treatment option for more than a decade in patients with advanced, unresectable HCC. However, there has been a dramatic change in the treatment algorithm in the last several years, given new drug approvals in the field. Most importantly, the combination of atezolizumab and bevacizumab has demonstrated clinically meaningful benefits in terms of response rate, progression-free survival, and overall survival compared to sorafenib in the first-line setting. Recently a phase III trial showed that the combination of durvalumab with a single dose of tremelimumab improved overall survival compared to sorafenib, while durvalumab monotherapy was found to be noninferior to sorafenib, making it an attractive alternative single agent in selected patient populations. As immunotherapy makes its way into the therapeutic landscape of HCC, other novel targeted therapies, such as lenvatinib, cabozantinib, ramucirumab, and regorafenib, have also been approved by regulatory authorities for treatment of advanced, unresectable HCC. This review article focuses on the first-line systemic treatment options for HCC while addressing some of the most important questions aimed at optimization of HCC treatment.

Keywords: hepatocellular carcinoma, advanced hepatocellular carcinoma

Introduction

Primary liver cancer, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma, is the sixth–most common cancer and the third-leading cause of cancer-related death worldwide, with >900,000 newly diagnosed cases and approximately 830,000 deaths in 2020.[1] In the US, from 2007 to 2016, the incidence of liver cancer was increasing by 2%–3% annually, with rapidly increasing mortality, which seems to have plateaued.[2,3] It is estimated that 41,260 new liver cancer cases will be diagnosed with 30,520 liver cancer–related deaths in the US in 2022, and liver cancer remains one of the malignancies with the lowest 5-year relative survival rate (18%), signifying the unmet need of improving therapeutic options for this dismal diagnosis.[2,3] However, a majority of HCC cases are potentially preventable given that the most common risk factors are modifiable (hepatitis B, hepatitis C, excess alcohol consumption, obesity, and tobacco use).[4]

The Barcelona Clinic Liver Cancer (BCLC) prognosis and therapeutic model, widely accepted internationally as the guidelines for HCC, incorporates disease staging, prognosis, and treatment recommendations based on characteristics of the tumor, patient performance status, and underlying hepatic reserve.[5] Surgical resection and liver transplantation are potential curative options for patients with very early–stage and early-stage HCC. Locoregional treatment, such as ablation, transarterial chemoembolization (TACE), transarterial radioembolization, and radiation, has been the main therapeutic method for intermediate stage (BCLC stage B) HCC, which is a heterogeneous group defined as patients with multinodular HCC who have preserved liver function and good performance status. Systemic treatment is the only option for patients with advanced stage (BCLC stage C) HCC with good performance status and Child–Pugh score A.[5] Sorafenib has been the only approved treatment for advanced HCC (BCLC stage C) since 2008, at which time it gained approval after demonstrating a survival benefit when compared to placebo,[6] until recent advances in systemic therapies redefining the treatment algorithm. We now have novel agents not only for advanced

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HCC, but which also may benefit patients with intermediate-stage HCC (BCLC stage B). In this review, we highlight the current and emerging systemic treatment options for HCC and propose a therapeutic model taking key patient-related factors into consideration.

First-Line Systemic Therapeutic Options

Tyrosine-Kinase Inhibitors

HCC is an arterial hypervascular tumor that most commonly arises from cirrhotic liver, which has a highly dysfunctional vascular microenvironment leading to tumor growth secondary to hypoxia-inducible factors.[7–9] VEGF plays a critical role in this dysfunctional angiogenesis, contributing to the tumorigenesis of HCC, which provides the rationale for HCC treatment targeting the VEGF pathway.

Sorafenib

Sorafenib is an antiangiogenic tyrosine-kinase inhibitor (TKI) that primarily targets the VEGF receptor (VEGFR), but also inhibits the PDGF receptor (PDGFR) and RAF. The SHARP study was an international, multicenter, double-blind, placebo-controlled, phase III trial that enrolled 602 patients with advanced HCC to receive either sorafenib (400 mg twice daily) or placebo. Sorafenib demonstrated significantly improved overall survival (OS; 10.7 vs 7.9 months, HR 0.69, 95% CI 0.55–0.87, $p<0.001$).[6] Although no difference was detected between the two cohorts in one of the primary end points, time to symptomatic disease progression (4.1 months vs 4.9 months, $p=0.77$), there was a significant difference in time to radiographic disease progression (5.5 months vs 2.8 months, $p<0.001$). Based on these results, the US Food and Drug Administration (FDA) approved sorafenib for patients with advanced HCC in November 2008. Meanwhile, a similar study specifically targeting the Asia–Pacific population was conducted and reported similar time to progression (2.8 vs 1.4 months, $p=0.0005$) and OS benefit (6.5 vs 4.2 months, HR 0.68, $p=0.014$), although the absolute median OS (mOS) was lower in both arms.[10] Sorafenib is overall well tolerated, with the most common side effects including weight loss, diarrhea, hand–foot syndrome, and hypophosphatemia. Sorafenib became the standard of care for advanced HCC for more than a decade. Table 1 lists all positive phase III systemic treatment studies for HCC.

Lenvatinib

Multiple studies failed to improve HCC clinical outcomes until lenvatinib, an antiangiogenic TKI targeting VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT, demonstrated its activity in advanced HCC in the phase III REFLECT trial. REFLECT was an open-label, international, noninferiority study comparing lenvatinib and sorafenib, which enrolled 954 patients with advanced HCC. The lenvatinib arm had mOS of 13.6 months compared to the sorafenib arm of 12.3 months, and the study met its primary end point of noninferiority in OS (HR 0.92, 95% CI 0.79–1.06, while the noninferiority margin was set at 1.08). Notably, median progression-free survival (mPFS) was 7.4 months in the lenvatinib arm compared to 3.7 months in the sorafenib arm (HR 0.66, 95% CI 0.57–0.77, $p<0.0001$).[11] Lenvatinib also led to higher response rates (40% vs 13%) than sorafenib and longer follow-up revealed that patients who had a response to lenvatinib had prolonged survival when compared to nonresponders (mOS 22.4 vs 11.4 months).[27] The most common side effects associated with lenvatinib included hypertension, diarrhea, decreased appetite, and weight loss. Based on the results of the REFLECT study, the FDA approved lenvatinib for first-line treatment of patients with unresectable HCC in August 2018.

Donafenib

Donafenib is a modified form of sorafenib with a trideuterated *N*-methyl group that improves the pharmacokinetic profile of the molecule. Donafenib inhibits VEGFR, PDGFR, and RAF kinase.[12] In a Chinese phase II/III study, 668 patients were randomized to donafenib or sorafenib with a primary end point of OS. This study was designed to test both the noninferiority and superiority of donafenib. Donafenib demonstrated superior OS (12.1 vs 10.3 months, HR 0.831, 95% CI 0.600–0.988, $p=0.0245$), while response rate and PFS were similar between arms.[12] Donafenib has a similar side-effect profile to sorafenib, but it was reported to have fewer drug-related adverse events than sorafenib (38% vs 50%, $p=0.0018$). Donafenib was approved in China, although it is not approved in the US.

Table 1 Selected phase III clinical studies with systemic treatment for hepatocellular carcinoma

	NCT	Study arm	Control arm	Patient numbers	Primary end point(s)	mOS (months)	HR	95% CI	*p*	FDA approval
First-line										
SHARP[6]	00105443	Sorafenib	Placebo	602	OS, time to symptomatic progression	10.7 vs 7.9	0.69	0.55–0.87	<0.001	Yes
Asia-Pacific[10]	00492752	Sorafenib	Placebo	226	Not predefined	6.5 vs 4.2	0.68	0.50–0.93	0.014	NA
REFLECT[11]	01761266	Lenvatinib	Sorafenib	954	OS	13.6 vs 12.3	0.92	0.79–1.06	NA	Yes
NA[12]	02645981	Donafenib	Sorafenib	668	OS	12.1 vs 10.3	0.831	0.699–0.988	0.0245	NA
CheckMate 459[13]	02576509	Nivolumab	Sorafenib	743	OS	16.4 vs 14.7	0.85	0.71–1.02	0.075	No[b]
IMbrave 150[14–16]	03434379	Atezolizumab–bevacizumab	Sorafenib	501	OS and PFS	19.2 vs 13.4	0.66	0.52–0.85	<0.001	Yes
Cosmic 312[17]	03755791	Atezolizumab–cabozantinib	Sorafenib	837	OS and PFS	15.4 vs 15.5	0.90	0.69–1.18[a]	0.44	No
Orient-32[18]	03794440	Sintilimab–IBI305	Sorafenib	595[c]	OS and PFS	Not reached vs 10.4	0.57	0.43–0.75	<0.0001	NA
HIMALAYA[19]	03298451	Tremelimumab–durvalumab	Sorafenib	1171	OS	16.43 vs 13.77	0.78	0.65–0.93	0.0035	Yes
NA[20]	03764293	Camrelizumab– apatinib	Sorafenib	543	OS and PFS	22.1 vs 15.2	0.62	0.49–0.80	<0.0001	No
RATIONALE 301[21]	03412773	Tislelizumab	Sorafenib	674	OS	15.9 vs 14.1	0.85	0.71–1.02	NA	No
Second-line										
Resorce[22]	01774344	Regorafenib	Placebo	573	OS	10.6 vs 7.8	0.63	0.50–0.79	<0.0001[d]	Yes
Celestial[23]	01908426	Cabozantinib	Placebo	707	OS	10.2 vs 8.0	0.76	0.63–0.92	0.005	Yes
Reach-2[24]	02435433	Ramucirumab	Placebo	292	OS	8.5 vs 7.3	0.71	0.531–0.949	0.0199	Yes
Keynote 240[25]	02702401	Pembrolizumab	Placebo	413	OS and PFS	13.9 vs 10.6	0.781	0.611–0.998	0.0238	Yes
Keynote 394[26]	03062358	Pembrolizumab	Placebo	453	OS	14.6 vs 13.0	0.79	0.63–0.99	0.0180	NA

Notes: [a]96.02% CI was reported in this study. [b]Was approved as second-line treatment, but voluntarily withdrawn after the negative phase III study. [c]Included 24 patients in the phase II safety run-in. [d]One-sided.
Abbreviations: NCT, National Clinical Trial; mOS, median overall survival; NA, not applicable; PFS, progression-free survival.

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Immunotherapy

Single-Agent Immunotherapy Options

The liver is the largest immunological organ with high exposure to neoantigens, and chronic inflammation plays a key role in HCC tumorigenesis. The PD1/PDL1 pathway and the CTLA4 axis are two critical immunocheckpoints in regulating normal liver function by promoting immunotolerance. However, in a chronic inflammatory state, these immunocheckpoints promote tumorigenesis by induction and maintenance of HCC immunotolerance via activation of regulatory T cells, resulting in immunosenescence.[28–30] Early phase I/II clinical studies with immunocheckpoint inhibitors (ICIs) in the second-line setting for advanced HCC showed promising clinical results with good tolerance, confirming the role of ICIs in advanced HCC treatment and leading to phase III studies in the first-line setting.[31,32]

Nivolumab

CheckMate 172 was an open-label, single-arm, phase I/II trial with a dose-escalation phase and a dose-expansion phase that enrolled 262 patients with advanced HCC (with or without sorafenib exposure, 48 in the dose-escalation phase and 214 in the dose-expansion phase). No dose-limiting adverse event was detected during the dose-escalation phase, and 3 mg/kg was chosen for dose expansion. In the dose-expansion phase, nivolumab (a PD1 inhibitor) monotherapy led to a 20% response rate with a median duration of response of 9.9 months. Importantly, the adverse-event profile seen in the HCC population was similar to that seen in other solid tumors treated with nivolumab.[32] Nivolumab subsequently received accelerated FDA approval as a second-line treatment after sorafenib.

CheckMate 459 was a confirmatory, international, open-label, phase III study comparing nivolumab with sorafenib in the first-line setting for patients with advanced HCC. The primary end point of the study was OS. Nivolumab led to mOS of 16.4 months compared to 14.7 months seen in the sorafenib arm (HR 0.85, 95% CI 0.72–1.02, p=0.075). The study's predefined significance level of p=0.0419 was not met.[13] As the CheckMate 459 study did not meet the prespecified primary end point, the US FDA Oncologic Drug Advisory Committee (ODAC) voted against (five to four) continuing the accelerated approval for nivolumab in the second-line setting, and the approval was subsequently voluntarily withdrawn by Bristol Myers Squibb.

Pembrolizumab

Pembrolizumab (a PD1 inhibitor) monotherapy first demonstrated its activity with a response rate of 18% in an international, multicenter, open-label, single-arm phase II study that enrolled 104 patients with advanced HCC who had received sorafenib previously.[31] Given the promising results, pembrolizumab received accelerated FDA approval for use as a second-line treatment in advanced HCC in November 2018. However, the subsequent randomized, double-blind, phase III trial KEYNOTE 240 that evaluated pembrolizumab as a second-line treatment option for advanced HCC did not meet its primary end points of OS and PFS (predefined one-sided significance thresholds p=0.002 at first interim analysis, p=0.0174 at final analysis). The KEYNOTE 240 study enrolled 413 patients with a 2:1 randomization ratio to either pembrolizumab or placebo. At the first interim analysis, pembrolizumab led to an mOS of 13.9 months compared to 10.6 months in the placebo arm (HR 0.781, 95% CI 0.611–0.998, p=0.0238) and mPFS of 3.0 months versus 2.8 months in the placebo arm (HR 0.718, 95% CI 0.570–0.904, p=0.0022). As such, OS and PFS in the KEYNOTE 240 trial did not reach prespecified statistical significance.[25] However, the FDA ODAC recommended continuing its accelerated approval (voted 9 to 0) given the potential benefit of pembrolizumab as a second-line treatment, especially for patients who are not candidates for first-line immunotherapy.

A similar phase III study, KEYNOTE 394, enrolled 453 patients with advanced HCC (Asian patients only) with a 2:1 randomization to pembrolizumab or placebo as second-line treatment. The primary end point of the study was OS with a predefined p-value boundary for OS superiority of 0.019 at final analysis. Pembrolizumab significantly improved mOS (14.6 vs 13.0 months, HR 0.79, 95% CI 0.63–0.99, p=0.0180). Pembrolizumab also improved response rate and PFS.[26] These data further supported the role of pembrolizumab as a second-line treatment option for advanced HCC in immunotherapy-naïve patients.

Tislelizumab

Tislelizumab (a PD1 inhibitor) was first evaluated in a phase II study (RATIONALE-208, NCT03419897) among 249 HCC patients with Child–Pugh A and BCLC stage B/C liver function who had received at least one prior line of therapy. Tislelizumab led to an overall response rate of 13.6% (95% CI 9.5%–18.7%). mPFS was 2.7 months (95% CI 1.6–2.8) and mOS was 13.5 months (95% CI 0.9–15.8).[33] As a result, RATIONALE 301, which was a global, phase III, randomized, open-label study conducted in Asia evaluating tislelizumab versus sorafenib in the first-line setting, was undertaken.[34] Final analysis of this trial was recently presented at the European Society for Medical Oncology (ESMO) Congress 2022, reporting that the study had met its primary end point of noninferior OS with mOS of 15.9 months with tislelizumab versus 14.1 months with sorafenib (HR 0.85, 95% CI 0.712–1.019, p=0.0398) among 674 patients.[21] Tislelizumab was associated with a higher response rate (14.3% vs 5.4%) and longer response duration (median 36.1 months vs 11.0 months), although mPFS was 2.2 months with tislelizumab compared to 3.6 months in the sorafenib arm. Tislelizumab was generally better tolerated than sorafenib, with fewer grade 3 or greater adverse events and fewer adverse events leading to discontinuation.

Immunotherapy with VEGF Inhibitors

As our knowledge on HCC tumorigenesis continued to evolve, VEGF was found to be an important immunomodulator by inhibiting dendritic and effector T-cell maturation, promoting immunosuppressive macrophages, enhancing immunocheckpoint molecule expression, decreasing adhesion molecule expression, and impairing IFNγ production by cytotoxic T cells.[35] As such, therapies targeting the VEGF pathway may reverse the immunosuppressive tumor microenvironment, and thus it is expected that the combination of ICIs with VEGF inhibitors would have synergistic effects, as seen in other solid tumors.[36]

Atezolizumab Plus Bevacizumab

GO30140 (NCT02715531) evaluated the role of atezolizumab in patients with advanced HCC. This international phase Ib trial consisted of five cohorts, with cohorts A and F targeting patients with advanced HCC. Patients in cohort A were treated with atezolizumab (a PDL1 inhibitor) plus bevacizumab (VEGF inhibitor), while patients in cohort F were randomized (1:1) to either atezolizumab monotherapy or atezolizumab plus bevacizumab. The combination of atezolizumab and bevacizumab led to a response rate of 36% (104 patients) in cohort A and mPFS of 5.6 months in cohort F (60 patients). mPFS was 3.4 months for atezolizumab monotherapy in cohort F (59 patients).[37]

Based on these pivotal study results, the global, open-label, phase III IMbrave 150 study directly compared the combination of atezolizumab plus bevacizumab to sorafenib (with a 2:1 randomization) as first-line treatment for patients with advanced HCC. The co–primary end points were OS and PFS. The prespecified HR for OS favoring atezolizumab–bevacizumab over sorafenib was 0.71 (p=0.002). At median follow-up of 8.6 months, mOS for the atezolizumab–bevacizumab arm was not able to be evaluated, but it was 13.2 months for the sorafenib arm (HR 0.58, 95% CI 0.42–0.79). mPFS was significantly prolonged in the atezolizumab–bevacizumab arm (6.8 vs 4.3 months, HR 0.59, 95% CI 0.47–0.76, p<0.001). Response rate was 27.3% in the atezolizumab–bevacizumab arm compared to 11.9% in the sorafenib arm (p<0.001).[14] With an additional 12 months of follow-up, updated mOS was 19.2 months with atezolizumab–bevacizumab vs 13.4 months with sorafenib. The updated objective response rate was 30% in the atezolizumab–bevacizumab arm.[16] The atezolizumab–bevacizumab regimen was well-tolerated in general, with the most common grade 3 or 4 event being hypertension. Of note, given the bleeding risk associated with bevacizumab, all patients in the study were required to undergo endoscopic evaluation within the 6 months prior to enrollment and varices must have been treated as per local standards of care.[14] The atezolizumab–bevacizumab combination also demonstrated favorable quality of life on prespecified patient-reported outcome analysis.[38] Given the outstanding results, the combination of atezolizumab and bevacizumab became the new standard first-line treatment for advanced HCC for patients who have BCLC B or C stage disease without contraindications.

Atezolizumab Plus Cabozantinib

Cabozantinib is a TKI targeting the VEGF pathway in addition to the Met and TAM family of kinases. Cabozantinib

initially demonstrated its antitumor activity in advanced HCC as monotherapy in the second-line setting in the randomized phase III CELESTIAL trial, and received FDA approval in January 2019.[23] Moreover, the combination of atezolizumab–cabozantinib showed clinical activity in a variety of solid tumors, making it an attractive combination in HCC.[39–41]

COSMIC 312 was an international, open-label, randomized, phase III trial comparing the combination of atezolizumab–cabozantinib to sorafenib as a first-line treatment for advanced HCC. The study randomized patients in a 2:1:1 ratio to atezolizumab–cabozantinib, sorafenib, or cabozantinib monotherapy. The primary end points were PFS in the first 372 patients assigned to the combination arm or sorafenib arm and OS in all patients in the combination arm and sorafenib arm. At the data cutoff on March 8, 2021, the first 837 patients were included in the analysis, with 432 in the combination arm and 217 in the sorafenib arm. No significant OS benefit was detected in the atezolizumab–cabozantinib arm compared to sorafenib (mOS 15.4 vs 15.5 months, HR 0.90, 95%, CI 0.69–1.18, p=0.44) and mPFS was longer in the atezolizumab–cabozantinib arm (mPFS 6.8 vs 4.2 months, HR 0.63, 95% CI 0.44–0.91, p=0.0012). Cabozantinib monotherapy led to longer mPFS than sorafenib (5.8 vs 4.3 months, HR 0.71, 95% CI 0.51–1.01, p=0.011). No new safety signal was detected. Of note, this study did not require endoscopic evaluation prior to enrollment; however, no excess serious bleeding events were seen in the cabozantinib-containing regimen, and the atezolizumab–cabozantinib combination arm had the lowest rate of grade 3 or higher hemorrhagic events.[17] Although the atezolizumab–cabozantinib regimen did not demonstrate OS benefit, it did show benefit in certain patient subgroups, including those with hepatitis B infection, extrahepatic disease, or macrovascular invasion, based on subgroup analysis.

Sintilimab Plus Bevacizumab Biosimilar (IBI305)

ORIENT-32 was an open-label, randomized, phase II/III study conducted in China. Twenty-four patients with advanced HCC were enrolled in the phase II safety run-in to receive sintilimab (a PD1 inhibitor) plus IBI305 (a bevacizumab biosimilar). In the phase III part of the study, 571 patients were randomized to either sintilimab–IBI305 or sorafenib. Co–primary end points were OS and PFS. With median follow-up of 10.0 months, sintilimab–IBI305 demonstrated improved PFS (4.6 vs 2.8 months, HR 0.56, 95% CI 0.46–0.70, p<0.0001) and OS (median not reached vs 10.4 months, HR 0.57, 95% CI 0.43–0.75, p<0.0001).[18] Given the promising results, the sintilimab–IBI305 combination was subsequently approved as a first-line treatment regimen in China.

Pembrolizumab Plus Lenvatinib

The combination of pembrolizumab and lenvatinib is an effective regimen in the first-line setting for renal cell carcinoma, as demonstrated in the phase III CLEAR trial.[42] This regimen also demonstrated encouraging clinical activity in advanced HCC in the single-arm phase Ib KEYNOTE 524 study. The pembrolizumab–lenvatinib combination led to a high objective response rate of 46% in 104 patients with mOS of 22 months.[43]

The combination of pembrolizumab–lenvatinib was subsequently evaluated in LEAP-002, a global, randomized, double-blind, phase III trial comparing this regimen to lenvatinib monotherapy in 794 patients with BCLC stage B or C HCC in the first-line setting.[44] At final analysis with median follow-up of 32.1 months, the study failed to meet its primary end points of improved OS (21.2 months vs 19.0 months, HR 0.84, 95% CI 0.708–0.997, p=0.0227) and mPFS (HR 0.867, 95% CI 0.734–1.024, p=0.0466) in the pembrolizumab–lenvatinib arm.[45]

Camrelizumab Plus Apatinib

The combination of camrelizumab (a PD1 inhibitor) with apatinib (a VEGFR2 TKI) demonstrated significant activity in the phase II RESCUE study that was conducted in China. The study included one cohort receiving this combination in the first-line setting and a second cohort receiving this drug in the second-line setting. At median follow-up of 29.1 months, mOS was 20.1 months in the first-line cohort (70 patients) and 21.8 months in the second-line cohort (120 patients).[46]

This combination was further evaluated in an international, open-label, randomized, phase III trial conducted in Asia, as first-line therapy for advanced HCC compared to sorafenib. Patients receiving camrelizumab plus apatinib demonstrated mPFS of 5.6 months versus 3.7 months with sorafenib (HR 0.52, 95% CI 0.41–0.65, p<0.0001) and mOS of 22.1

months versus 15.2 months with sorafenib (HR 0.62, 95% CI 0.49–0.80, $p<0.0001$), and the study reached its primary end points of improved PFS and OS.[20]

Combination Immunotherapy Regimens

CTLA4 and PD1/PDL1 are two crucial components playing distinct roles in the regulation of adaptive immunity: CTLA4 inhibits early T-cell activation during the priming process, while PD1/PDL1 induces T-cell exhaustion. Combination therapy with anti-CTLA4 and anti-PD1/PDL1 has improved clinical outcomes in various solid tumors, supporting the synergistic effect of this combination.[47]

Nivolumab Plus Ipilimumab

The combination of ipilimumab (anti-CTLA4 antibody) with nivolumab (anti-PD1 antibody) for management of HCC was first tested in the three-arm CheckMate 040 study. This was a global, multicenter, open-label, phase I/II study. Patients with advanced HCC with prior exposure to sorafenib were randomized (1:1:1 ratio) to nivolumab–ipilimumab combination treatment with different dosing schedules (arm A, ipilimumab 3 mg/kg plus nivolumab 1 mg/kg every 3 weeks for four doses followed by nivolumab 240 mg every 2 weeks; arm B, ipilimumab 1 mg/kg plus nivolumab 3 mg/kg every 3 weeks for four doses followed by nivolumab 240 mg every 2 weeks; arm C, ipilimumab 1 mg/kg every 6 weeks plus nivolumab 3 mg/kg every 2 weeks). A total of 148 patients were enrolled in the study (50 in arm A, 49 each in arm B and C). Although all therapeutic strategies resulted in similar overall response rates (32% vs 27% vs 29%), mOS was significantly longer in arm A (22.8 vs 12.5 vs 12.7 months, respectively), favoring the higher dose of ipilimumab (3 mg/kg) for four doses combined with nivolumab. Of note, arm A also had a higher rate of treatment-related adverse events.[48] The arm A regimen received accelerated FDA approval for patients with advanced HCC who had previously received sorafenib treatment. The confirmatory phase III study (CheckMate 9DW, NCT04039607) comparing ipilimumab plus nivolumab versus sorafenib or lenvatinib for treatment-naïve advanced HCC is ongoing.

Durvalumab Plus Tremelimumab

Durvalumab (a PDL1 inhibitor) and tremelimumab (a CTLA4 inhibitor) combination was first studied as a second-line treatment for advanced HCC in a phase I/II study. A total of 332 patients were randomized to one of four arms (T300+D arm, tremelimumab 300 mg plus durvalumab 1500 mg for one dose followed by durvalumab 1500 mg once every 4 weeks, later named single tremelimumab regular interval durvalumab [STRIDE] regimen; D arm, durvalumab 1500 mg every 4 weeks; T arm, tremelimumab 750 mg once every 4 weeks; T75+D arm, tremelimumab 75 mg plus durvalumab 1500 mg once every 4 weeks for four doses followed by durvalumab 1500 mg once every 4 weeks). The T300+D (STRIDE) arm led to the most encouraging benefits, with an overall response rate of 24% and mOS of 18.7 months (compared to RR of 10.6%, 7.2%, and 9.5% and mOS of 13.6, 15.1, and 11.3 months, respectively, in the D arm, T arm, and T75+D arm).[49]

The HIMALAYA study was a global, open label, randomized, phase III trial evaluating the STRIDE regimen and durvalumab monotherapy versus sorafenib as first-line treatment in advanced HCC. Of note, this study was slightly different from other immunotherapy trials in that patients with main portal vein invasion were excluded. The primary end point was OS for the STRIDE regimen versus sorafenib and a secondary end point was noninferiority for OS for durvalumab versus sorafenib. mOS was 16.4 months with the STRIDE regimen (393 patients), 16.56 months in the durvalumab monotherapy arm (389 patients), and 13.77 months in the sorafenib arm (389 patients). The OS HR of the STRIDE regimen vs sorafenib was 0.78 (96.02% CI 0.65–0.93, $p=0.0035$) and for durvalumab monotherapy vs sorafenib was 0.86 (95.67% CI 0.73–1.03, noninferiority margin 1.08). The study met its prespecified primary end point and secondary end point, although PFS was not significantly different among the three groups.[19] The FDA granted priority review for the STRIDE regimen and durvalumab monotherapy in advanced HCC in April 2022 based on the HIMALAYA study results.

Second-Line Systemic Treatment

All currently available FDA-approved second-line treatment options for advanced HCC were approved in the era of sorafenib as the only first-line systemic option, so a placebo is commonly used as a control in these studies. Most patients

enrolled in these second-line studies had Child–Pugh A liver disease and ECOG status 0–1. As mentioned, single-agent immunotherapeutic agents (nivolumab and pembrolizumab) were approved by the FDA as second-line treatment for advanced HCC based on single-arm, open-label, early-phase study results.[31,32] Nivolumab indication was voluntarily withdrawn after the negative phase III first-line CheckMate 459 study, while pembrolizumab had conflicting results from two phase III second-line studies (KEYNOTE 240 and KEYNOTE 394) and remains approved in the US.[25,26] There are also several other FDA-approved second-line treatment options based on survival benefits seen in phase III clinical trials. However, there have been no trials comparing outcomes between these treatment options.

Regorafenib

Regorafenib is an oral TKI targeting VEGFR, PDGFR, RET, c-Kit, the angiopoietin 1 receptor, and FGFR1. The RESORCE study was a randomized, double-blind, placebo-controlled, phase III international study that compared regorafenib to best supportive care in 573 patients with advanced HCC that had tolerated and progressed on sorafenib, with OS as the primary end point. Only patients that had tolerated previous sorafenib treatment (≥20 days of last 28 days of treatment) were allowed to participate. Regorafenib improved OS, with a HR of 0.63 (10.6 vs 7.8 months, 95% CI 0.50–0.79, one-sided $p<0.0001$) with a reasonable side-effect profile, the most common being hypertension, hand–foot syndrome, fatigue, and diarrhea.[22] This led to FDA approval of regorafenib as a second-line treatment for patients with advanced HCC who had tolerated but progressed on first-line sorafenib in April 2017.

Cabozantinib

Cabozantinib is a TKI targeting VEGFR1–3, Met, and the AXL pathway. The randomized, double-blind, phase III CELESTIAL study enrolled 707 patients with HCC who had had disease progression on sorafenib (may have received up to two previous systemic treatments). The primary end point was OS. Patients were randomized in a 2:1 ratio to either cabozantinib or placebo. Cabozantinib treatment led to significantly better OS than placebo (10.2 vs 8.0 months, HR 0.76, 95% CI 0.63–0.92, $p=0.005$). The most common adverse events in the cabozantinib arm were hand–foot syndrome, hypertension, AST elevation, fatigue, and diarrhea.[23] Subsequently, the FDA approved its use as a second-line treatment in March 2019.

Ramucirumab

Ramucirumab, a VEGFR2 inhibitor, demonstrated its antitumor activity in biomarker-selected patients with advanced HCC who had had previous sorafenib treatment with α-fetoprotein (AFP) concentration of 400 ng/mL or higher. The REACH-2 study was a randomized, double-blind, global, phase III study with patients randomized to ramucirumab or placebo (2:1 ratio) with a primary end point of OS. mOS was significantly prolonged with ramucirumab compared to placebo (8.5 vs 7.3 months, HR 0.710, 95% CI 0.531–0.949, $p=0.0199$). Most common grade 3 adverse events in the ramucirumab arm were hypertension, hyponatremia, and AST elevation.[24] Ramucirumab received US FDA approval as a second-line treatment option in May 2019 for patients with advanced HCC who have AFP ≥400 ng/mL.

Treatment Algorithm for Advanced HCC

Since sorafenib gained FDA approval as the first systemic treatment after demonstrating survival benefit in HCC, it has taken more than a decade to identify another effective systemic treatment that is superior to sorafenib for advanced HCC.[6,22] However, with the advancement of our knowledge regarding tumorigenesis in HCC, we now have more than ten treatment options when we consider all first- and second-line options supported by phase III clinical trials (Table 1). However, one of the major challenges is to identify the right sequence of therapy based on the overall clinical status of patients, especially in the absence of predictive biomarkers that guide us in selecting the best regimen for each patient.[50] We propose the following treatment algorithm based on the data to date (Figure 1).

We should first carefully evaluate patient characteristics. All phase III advanced HCC studies enrolled BCLC stage B or C patients with well-preserved liver function (Child–Pugh class A) and good performance status (ECOG performance status 0–1), so in theory only these patients may be considered eligible for systemic treatment, although there is limited evidence showing patients with Child–Pugh B score may still benefit from treatment. Immunotherapy is

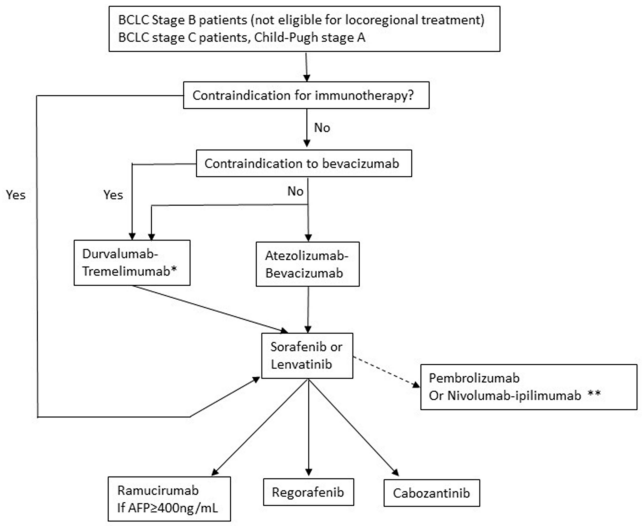

Figure 1 Proposed treatment algorithm for advanced HCC patients who are eligible for systemic treatment.
Notes: *This regimen was FDA-approved recently. **Only for patients who do not have contraindications for immunotherapy, but have not received immunotherapy in first-line setting. Alternative options that may be considered in the future include camrelizumab–apatinib and tislelizumab, with recent studies demonstrating survival benefit and noninferiority compared to sorafenib, respectively.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein.

contraindicated for patients who have moderate to severe autoimmune disease or patients who have had organ transplantation. Bevacizumab is associated with increased risk of gastrointestinal bleeding, so varices should be evaluated through endoscopy and treated before starting treatment. Moreover, bevacizumab is also contraindicated for patients with severe active cardiovascular disease or kidney dysfunction.

Details of each treatment regimen should also be taken into consideration. For example, ramucirumab only demonstrated survival benefit in HCC patients with AFP ≥400 ng/mL while regorafenib was studied in patients who had good tolerance of sorafenib.[22,24] Another important factor that needs special consideration is the cost of therapies, in order to avoid financial toxicity based on insurance coverage. All TKIs are oral medications that may lead to high copayment, while infusional treatments usually have better coverage but lead to time/transportation burden for the patients and their families. The high cost of TKIs has been associated with decreased adherence in other malignancies.[51,52] However, it is important to note that most drug companies offer patient-assistance programs for oral TKIs to offset therapy-related costs for eligible patients.

Atezolizumab–bevacizumab (IMbrave 150 study) has the best mOS and RR in all phase III studies among FDA-approved therapies, and should be considered standard of care as the first-line treatment for eligible patients that do not have any contraindication to immunotherapy or bevacizumab.[14] Recently, camrelizumab–apatinib has shown survival benefit in the first-line setting, although this regimen has not yet received FDA approval.[20] For patients who do not have a contraindication to immunotherapy but cannot take bevacizumab, the STRIDE regimen consisting of durvalumab and tremelimumab could be considered based on the HIMALAYA study results.[19] In addition, patients who may not have timely access to endoscopy could also potentially be considered for the STRIDE regimen, although endoscopy may not be necessary in certain patients with liver-stiffness measurement <20 kPa and platelet count >150×10^9/L as per BAVENO VII recommendations.[53,54] An alternative option may be tislelizumab, which has demonstrated noninferiority to sorafenib in the first-line setting, although this is not yet FDA-approved.[21] Following progression, patients may be considered for single-agent ICIs like pembrolizumab or dual-agent immunotherapy, such as nivolumab–ipilimumab. Other options would include cabozantinib, regorafenib, and ramucirumab, although these agents, with the exception of cabozantinib, were studied only after progression on sorafenib (there were 17 patients who had had prior immunotherapy enrolled in the CELESTIAL study, and cabozantinib showed clinical activity and tolerability in these patients).[55] For patients who have contraindications to immunotherapy, first-line treatment options include sorafenib or lenvatinib, followed

by second-line options that may include cabozantinib,[23] regorafenib (if there is good tolerance to sorafenib in the first-line setting),[22] or ramucirumab (if AFP ≥400 ng/mL).[24]

As mentioned previously, at present we do not have reliable predictive biomarkers for us to use in selecting a treatment regimen. However, it may be reasonable to consider regimens that target alternate tumorigenic pathways upon progressive disease. For example, with an event of progressive disease with the combination of atezolizumab–bevacizumab previously, ramucirumab in the second-line setting may not be ideal, as both bevacizumab and ramucirumab are agents that target the VEGF angiogenic pathway. It might be better to choose a medication with fewer overlapping targets, as outlined in Table 2.

Our proposed treatment algorithm is consistent with current NCCN guidelines in recognizing atezolizumab–bevacizumab as the preferred first-line option for advanced HCC. NCCN guidelines list pembrolizumab and durvalumab as alternative first-line options; however, we do not emphasize this within our algorithm, as pembrolizumab has had mixed results in clinical trials, and while durvalumab monotherapy has demonstrated noninferiority to sorafenib, the STRIDE regimen has demonstrated survival benefit over sorafenib and may therefore be preferred. Our algorithm is consistent with current ESMO guidelines.

The Role of Systemic Treatment in Earlier-Stage HCC

For patients with early-stage HCC (BCLC stage 0 and A), surgical resection and ablation are the treatments of choice. Adjuvant antiviral treatment for hepatitis-related HCC demonstrated benefit for those who had active viral infections.[64,65]

Table 2 Targets in hepatocellular carcinoma by different treatments

	VEGF	PD1/PDL1	CTLA4	RAF	PDGFR/c-Kit	FGFR	RET	Met	AXL/FLT3/TRKB	TIE2
Bevacizumab[56]	X									
Apatinib[57]	X									
Ramucirumab[58,59]	X									
Atezolizumab[14]		X								
Pembrolizumab[25]		X								
Durvalumab[19]		X								
Camrelizumab[60]		X								
Tislelizumab		X								
Nivolumab[61]		X								
Sintilimab[62]		X								
Ipilimumab[63]			X							
Tremelimumab[19]			X							
Sorafenib[6]	X			X	X					
Lenvatinib[11]	X				X	X	X			
Donafenib[12]	X			X	X					
Regorafenib[22]	X			X	X	X	X			X
Cabozantinib[17]	X						X	X	X	X

Abbreviations: VEGF, vascular endothelial growth factor; PD-1/PD-L1, programmed death protein-1/programmed death protein-Ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; RAF, rapidly accelerated a fibrosarcoma; PDGFR/c-Kit, platelet-derived growth factor receptor/tyrosine-protein kinase KIT; FGFR, fibroblast growth factor receptor; RET, rearranged during transection; MET, receptor tyrosine kinase MET; AXL/FLT3/TRKB, receptor tyrosine kinase AXL/FMS like tyrosine kinase-3/tyrosine receptor kinases B; TIE2, tyrosine kinase with immunoglobulin-like loops and epithelial growth factor homology domain-2.

TACE has been used widely in China as adjuvant treatment after curative surgery, but evidence supporting its use is limited.[66,67] Since sorafenib demonstrated its activity in advanced HCC, there has been a hypothesis that sorafenib in addition to locoregional therapy may lead to survival benefits in patients with early-stage HCC. The phase III STORM study enrolled 1114 patients with HCC who had curative-intent surgical resection or ablation and randomized these patients to either sorafenib or placebo. Sorafenib did not demonstrate any OS benefit (HR 0.99, 95% CI 0.76–1.30). Unfortunately, no significant improvement in time to recurrence or recurrence-free survival was observed either.[68] Several randomized/nonrandomized studies (including a phase III Asian trial) failed to demonstrate any OS or PFS benefit when adding sorafenib to TACE.[69,70] Given the different mechanisms and better clinical activity of novel agents now available for advanced HCC, there has been resurgent interest in testing the role of systemic treatment in early-stage HCC (as adjuvant treatment, monotherapy compared to TACE, or in combination with TACE).

LAUNCH was a randomized, open-label, phase III study conducted in China. A total of 338 patients with advanced HCC were randomized (1:1 ratio) to either lenvatinib plus TACE (LEN-TACE arm) or lenvatinib alone (LEN arm). Adding TACE to lenvatinib significantly improved mOS, which was the study's primary end point (17.8 vs 11.5 months, HR 0.45, 95% CI 0.33–0.61, $p<0.001$). Grade 3–4 liver enzyme elevation and hyperbilirubinemia were more frequently seen in the LEN-TACE arm.[71] This study result is encouraging, and other ongoing studies further evaluating this approach will give us more evidence. Table 3 lists some of these ongoing phase III studies investigating the role of systemic treatment in earlier-stage HCC.

Table 3 Selected phase III studies determining the role of systemic treatment in earlier-stage hepatocellular carcinoma

	NCT number	Patient numbers	Study arm	Control arm	Primary end points
IMbrave050	04102098	668	Atezolizumab + bevacizumab	Active surveillance	RFS
EMERALD-2	03847428	877	Durvalumab + bevacizumab	Placebo	RFS
			Durvalumab		
CHECKMATE 9DX	03383458	545	Nivolumab	Placebo	RFS
KEYNOTE 937	03867084	950	Pembrolizumab	Placebo	RFS
ABC-HCC	04803994	434	Atezolizumab + bevacizumab	TACE	TTF
RENOTACE	04777851	496	Regorafenib + nivolumab	TACE	PFS
TACE-3	04268888	522	Nivolumab + TACE	TACE	OS, TTTP*
LEAP-012	04246177	950	Pembrolizumab + lenvatinib + TACE	TACE	PFS, OS
CHECKMATE 74W	04340193	765	Nivolumab + ipilimumab + TACE	TACE	TTTP, OS
			Nivolumab + TACE		
EMERALD-1	03778957	724	Durvalumab + bevacizumab + TACE	TACE	PFS
			Durvalumab + TACE		
EMERALD-3	05301842	525	Durvalumab + tremelimumab + lenvatinib + TACE	TACE	PFS
			Durvalumab + tremelimumab + TACE		

Note: *TTTP was the primary end point for the phase II part.
Abbreviations: NCT, National Clinical Trial; RFS, recurrence-free survival; TACE, transarterial chemoembolization; TTF, time to treatment failure; PFS, progression-free survival; TTTP, time to TACE progression.

Conclusion

A number of novel agents have gained approval for the treatment of HCC over the last decade, with the strongest evidence supporting upfront atezolizumab–bevacizumab combination, with durvalumab–tremelimumab also demonstrating its OS benefit in a phase III study. Recent studies have also shown efficacy of camrelizumab–apatinib and tislelizumab in the first-line setting. Sorafenib and lenvatinib are first-line treatment options for patients who have contraindications to immunotherapy, while regorafenib, cabozantinib, ramucirumab, and pembrolizumab are approved after sorafenib exposure. Ongoing clinical trials focusing on such areas as the optimal sequence of treatment, role of immunotherapy in earlier-stage disease, treatment for patients with suboptimal liver function, and novel agents/combinations for advanced HCC will lead to better clinical outcomes for patients with HCC.

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